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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,963	03/09/2006	Andrew Chee-Yuen Chan	11669.0150USW1	1445

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,963	CHAN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *11-15, 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-10, 16-18, is acknowledged. The traversal is on the ground(s) that groups I-V are classified in the same search class and that a search of these claims can be made without serious burden. This is not found persuasive because firstly, groups I-V do not classify in the same class or subclass. Even those that do, the different methods have different method steps, measuring different criteria, and require separate search and considerations, and thus there is a search burden to examine all the groups together. However, as indicated previously, once the product claims are found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder.

The searches for groups II-V and I may have certain overlap, but they are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-22 are pending, however, claims 11-15, 19-22 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-10, 16-18 are under current examination.

Claim Objections

Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 8 depends from claim 7, which is drawn to receptors expressed on the surface of leucocytes, whereas claim 8 covers receptors on cells beyond leucocytes, the scope is broader than the previous claim 7. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse whose genome comprises a nucleic acid encoding a) human CD20 and b) alpha chain subunit A of human CD16, operably linked to the corresponding endogenous promotes, and further comprising disruptions of the corresponding endogenous gene, does not reasonably provide enablement for making a transgenic *animal* beyond the mouse whose genome comprises a nucleic acid encoding human CD20 and any subunit of a heterologous FcγIII receptor (CD16), operably linked to any endogenous promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims broadly encompass any transgenic animal whose genome comprises a nucleotide encoding human CD20 and a subunit of any heterologous FcγIII receptor. Although the specification teaches generating transgenic mice whose genome comprises a polynucleotide encoding a human CD20, and alpha chain subunit A of human CD16, it only contemplates that such method applies to other animals, or other animal species could be produced with art known methods. The specification provides a working example, i.e. making a mouse expressing human CD20 using microinjection technique, wherein the human CD20 coding sequence was randomly inserted into the genome of the mouse, and then through successively mating and crossing with mice having human CD16 alpha chain and lacking CD16 alpha chain, generated mice expressing both CD20 and CD16 alpha chain subunit A. However, the specification fails to provide teachings or guidance with regard to the efficiency of producing other animal species as claimed, and it would have required undue experimentation for one of skill for an attempt to produce transgenic non-human animals for the breadth claimed given the state of the art and unpredictability in the art. This is because microinjection produces transgenic animals having randomly inserted transgene sequence in their genome, and the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms, which prevent expression of the transgene, such as DNA methylation or deletion from the genome (*Kappell et al*, Current Opinion in Biotechnology 1992;3:548-53, page 549, col. 2, parag. 2). *Mullins et al* (1993) states that not all animals express a

transgene sufficiently to provide a desired phenotype as the integration of a transgene into difference species of animal has been reported to give divergent phenotypes (*Mullins et al* 1993, Hypertension 22:630-3, page 631, col. 1, parag. 1, lines 14-17). *Hammer et al* (J Anim Sci 1986;63:269-78) report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (*Houdebine*, J. Biotech. 1994;34:269-87, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (*Wall* 1996, Theriogenology 45,57-68, page 61, parag. 2, line 9 to page 62, line 3). *Wall et al* (J Dairy Sci 1997;80:2213-24) further report that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph). *Mullins et al* disclose that "THE USE OF NONMURINE SPECIES FOR TRANSGENESIS WILL CONTINUE TO REFLECT THE SUITABILITY OF A PARTICULAR SPECIES FOR THE SPECIFIC QUESTIONS BEING ADDRESSED, BEARING IN MIND THAT A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER." (*Mullins et al*, J. Clin. Invest. 1996 ;98 :S37-40, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (*Cameron*, Molec. Biol. 1997;7:253-65, page 256,

col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (*Cameron* 1997, Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (*Cameron* 1997, Molec. Biol. 7, page 256, lines 10-13). Further, *Sigmund* (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (*Sigmund*, Arteroscler. Throm. Vasc. Biol. 2000;20:1425-9, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, *Niemann* (1998) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (*Niemann*, Transg. Res. 1998;7:73-5, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). *Wilmut* (Cloning Stem Cell 2003;5:99-100) teaches, "BY THE TIME OF DOLLY'S DEATH IN 2003, CLONES HAD BEEN DERIVED FROM ADULT CELLS OF SEVERN MAMMALIAN SPECIES, BUT THE SAME TECHNIQUES WERE NOT SUCCESSFUL IN SEVEN OTHERS, DESPITE INTENSIVE EFFORTS BY EXPERIENCED RESEARCH TEAMS. THESE INCLUDE RHESUS MONKEY, RAT, DOG, AND HORSE. THIS FAILURE EMPHASIZES THE IMPORTANCE OF DIFFERENTCES BETWEEN SPECIES. THE DIFFERENCE MIGHT BE IN THE MOLECULAR MECHANISMS THAT REGULATE EARLY DEVELOPMENT OR IN ENABLING TECHNIQUES FOR OOCYTE RECOVERY, EMBRYO CULTURE, OR EMBRYO TRANSFER. SUCH DIFFERENCES HAVE ALREADY BEEN IDENTIFIED BETWEEN THE SPECIES FROM WHICH CLONES HAVE BEEN DERIVED" (emphasis added).

Moreover, since the CD20-CD16 transgenic mouse was produced by mating and crossing with a heterologous CD16-expressing mouse, production of other transgenic animals expressing both CD20 and CD16 requires the availability of another animal expressing a heterologous CD16. Since it was not known that such animals exist, practicing instant invention would require production of at least two types of transgenic animals, expressing either CD20 or CD16, and subsequent crossing. Given the inefficiency in generating large animals, the claimed invention would require undue experimentation.

The state of the art of making transgenic animal other than mouse is an inefficient process, the commonly used methods are homozygous DNA recombination using embryonic stem cells (ES cells), pronuclear microinjection of genetic material, and genetically modified somatic cell nuclear transfer (SCNT). Among them, the most efficient means of obtaining a transgenic animal is through homozygous recombination in embryonic stem cells (ES cells). Unfortunately, the state of the art is such that ES cell technology is generally limited to the mouse system at present, (see *Moreadith et al*, J. Mol. Med., 1997 Mar;75(3):208-16, p. 214, Summary and also *Pera et al,* Journal of Cell Science 2000;113: 5-10), and thus pronuclear microinjection and nuclear transfer of genetically modified nuclear material to somatic cells have to be used for producing transgenic animals beyond mouse. While microinjection has been used since early years, it is highly inefficient. *Logan et al* (Clin Exp Pharmacol Physiol 1999;26:1020-5) estimate, "THE FREQUENCY OF TRANSGENIC ANIMALS OBTAINED FROM THIS PROCESS [MICROINJECTION] IS LOW, USUALLY APPROXIMATELY 1% OR LESS OF MICROINJECTED TRANSFERRED

EGGS"; among the 1% or less that succeed to mature, "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN ANIMALS HAVE BEEN RELATED TO INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATION, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN ORGAN WILL EXPRESS THE GENE" (column 2, page 1021). Microinjection often produce mosaic transgenic animal wherein only a portion of cells/organ express the transgene. Further, the time and cost of screening for germline transmission in these mosaic animals could be prohibitive to generating more transgenic animals through breeding. This is why, in recent years, the attentions have shifted to using genetically modified somatic cell nuclear transfer technology for producing transgenic livestock.

In view of the state of the art pertaining to making transgenic animal through somatic NT cloning, it is still in its infant stage, even without further genetic modification, the faulty epigenetic reprogramming of donor cell genome have lead to major dysregulation of gene expression and high mortality of the cloned offspring, and thus when the additional transgene manipulation and screening are added to the process, it would be more difficult to routinely obtain a desired nonhuman mammal expressing a transgene of interest. *Denning* (Nat Biotech 2001;19:559-562) teaches difficulties of genetic manipulation and somatic cell cloning, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560). *Dr. Wilmut*, a pioneer in animal cloning, teaches "THE MOST STRIKING THING ABOUT THE TECHNIQUES THAT EMERGED DURING DOLLY'S LIFE IS THAT MAMMALIAN CLONING

REMAINS A REPEATABLE, BUT INEFFICIENT PROCEDURE. IT IS STILL TRUE THAT ONLY 1-5% OF RECONSTRUCTED EMBRYOS DEVELOP TO BECOME VIABLE OFFSPRING, REGARDLESS OF VARIATIONS IN SPECIES, CELL TYPE, OR NUCLEAR TRANSFER PROTOCOL. THIS LOW OVERAL SUCCESS RATE IS THE CUMULATIVE EFFECT OF FAILURE AT ALL STAGES OF DEVELOPMENT, INCLUDING AFTER BIRTH. AN EXTRAORDINARY VARIATIY OF ABNORMALITIES HAVE BEEN DESCRIBED IN CLONED FETUSES AND OFFSPRING." And "THIS OUTCOME HAS BEEN ASSOCIATED WITH VERY GREAT VARIATION IN GENE EXPRESSION IN CLONED EMBRYOS, FETUSES, AND OFFSPRING" (Cloning Stem Cells 2003;5:99-10, see mid-section of column 2, page 99, emphasis added). *Smith and Murphy* (Cloning Stem Cells 2004;6:126-32) point to the underlying reasoning why genetic and epigenetic variations occurred, the mechanism about how the host cytoplasm and donor nuclei interact to produce a developmentally competent reconstructed embryo is largely unknown. *Smith and Murphy* teach, apart from the major chromosomal anomalies found in developmentally arrested embryos and fetuses, less detrimental rearrangements and/or mutations are likely to go unnoticed in most donor cell karyotypes, which could lead to inheritable anomalies among clones and their offspring. *Smith and Murphy* go on to teach that the variations may come from the donor nuclear DNA sequence, the mitochondrial DNA from the host oocyte, and epigenetic alterations to the DNA or to the histone packaging proteins. *Polejaeva et al* (Nature 2000;407:86-90) teach, "TO DATE, THE EFFICIENCY OF SOMATIC CELL NUCLEAR TRANSFER, WHEN MEASURED AS DEVELOPMENT TO TERM AS A PROPORTION OF OOCYTES USED, HAS BEEN VERY LOW (1-2%). A VARIETY OF FACTORS PROBABLY CONTRIBUTE TO THIS INEFFICIENCY THESES INCLUDE LABORATORY TO LABORATORY VARIATION, OOCYTE SOURCE AND QUALITY, METHODS OF EMBRYO CULTURE, DONOR CELL TYPE, POSSIBLE LOSS OF SOMATIC IMPRINTING IN THE NUCLEI OF THE RECONSTRUCTED EMBRYO, FAILURE

TO REPROGRAM THE TRANSPLANTED NUCLEUS ADEQUATELY, AND FINALLY, THE FAILURE OF ARTIFICIAL METHODS OF ACTIVATION TO EMULATE REPRODUCIBLY THOSE CRUCIAL MEMBRANE-MEDIATED EVENTS THAT ACCOMPANY FERTILIZATION" (1st paragraph). *Simerly et al* (Science 2003;300:297) report the molecular obstacles in cloning primates, and conclude, "PRIMATE NUCLEAR TRANSFER APPEARS TO BE CHALLENGED BY STRICTER MOLECULAR REQUIREMENTS FOR MITOTIC SPINDLE ASSEMBLY THAN IN OTHER MAMMALS", AND "WITH CURRENT APPROACHES, NT TO PRODUCE EMBRYONIC STEM CELLS IN NONHUMAN PRIMATES MAY PROVE DIFFICULT—AND REPRODUCTIVE CLONING UNACHIEVABLE". Apparently, it was not, and has yet to become routine in the art to obtain a nonhuman transgenic animal beyond mouse expressing a desired transgene such as CD20 and CD16. The skilled in the art intending to practice the claimed invention would have to carry out undue experimentation to make the required non-human transgenic mammals while the efficiency of the process would be expected low (<=1%) and phenotypic outcome of the animal is unpredictable due to the variation in transgene expression in cells/organs as discussed *supra*.

While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene and inefficiency in the art, and when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises a human CD20 and CD16, other than the exemplified transgenic mouse, it would have required undue experimentation to obtain any given laboratory animal comprising and expressing a hCD20 and a hCD16. Since the specification fails to disclose representative species of

transgenic animals encompassed by the claims there is no way to predict the outcome of the claimed invention. Accordingly, it is concluded that the specification fails to provide an enabling disclosure to support the full scope of the claimed invention.

The claims as written embrace transgenic animals wherein the CD20 and/or CD16 are operably linked to any given endogenous promoter. However, since CD20 and CD16 are preferentially expressed in certain cell types as indicated in claims 7 and 8, only the CD20 or CD16 endogenous promoters would achieve such cell-specific expression.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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PRIMARY EXAMINER

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QJL
September 4, 2007